THE EXTRA-RENAL SEQUEL TO EXPERIMENTAL RENAL HYPERTENSION*

ERIC OGDEN

Professor of Physiology, University of Texas, Medical Branch, Galveston, Texas
Visiting Professor of Physiology, New York University School of Medicine

THE recently revived interest in the study of experimental hypertension has been largely directed toward understanding the etiology of hypertension as seen in man, especially essential hypertension, and toward producing this disease experimentally for further study. Although neither of these intentions has been crowned with direct success, our understanding of the circulation, both normal and hypertensive, has been greatly increased by these studies, and particularly those initiated by Goldblatt's[1] work on clamping the renal artery. So it seems worthwhile to consider experimental hypertension as a field of study in itself and to review some of the observations in an attempt to evaluate changing concepts in the field.

EXPERIMENTAL HYPERTENSION OF CEREBRAL ORIGIN

Since the cerebral cortex is dependent upon an immediate blood supply, and the carotid and vertebral arterial systems seem specially designed to guard it, one might expect that an interference with the proper delivery of blood to the brain would produce a compensatory rise in blood pressure. That this is not a simple arrangement is clear since intracranial vascular disease usually does not produce chronic arterial hypertension unless there is an accompanying change in intracranial pressure.

This question has been approached experimentally by Nowak and his colleagues[2] who found that successive ligation of the various cerebral arteries is sometimes followed by chronic hypertension, but Blalock and Levy[3] produced only temporary hypertension by this means.

Dixon and Heller[4] using dogs, and Griffith, Jeffers and Lindauer[5] using rats, produced sustained hypertension by raising the intracranial pressure by the intracisternal injection of kaolin. Griffith and Roberts[6]

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found about four-fifths of rats or dogs so injected became hypertensive. The inflammatory reaction and leukocytosis resulting from these injections had usually begun to subside before the hypertension appeared. This observation is in contrast to the prompt rise of blood pressure which occurs in man as the intracranial pressure rises. Reports indicate somewhat variable results with this method; Blalock in his review[7] expresses the belief "that this type of hypertension cannot be produced with great regularity and that the elevation of blood pressure is usually not persistent." At the present time it may be said that there is no clear indication that studies of cerebral ischemia by arterial ligation or the injection of kaolin have shed much light on the etiology of human hypertension except that which follows injuries, tumors, and other causes of raised intracranial pressure. Nor has there been a sufficiently varied or extensive study made of animals hypertensive from these causes to add considerably to our knowledge of the behavior of organisms as a whole, or of various organs within them, when subjected to a period of raised blood pressure.

At this time a careful experimental study of cerebrospinal fluid pressure in animals with Goldblatt hypertension might be fruitful.

Hypertension From Vitamin D and Desoxycorticosterone

The association of elevated systolic blood pressure with raised blood cholesterol and arteriosclerosis led to the experiments in which Appelrot[8] studied the possible hypertension-producing effect of Vitamin D_2. The data are insufficient to add much to our knowledge of hypertensive processes; but Handovsky[9] reports that dogs whose blood pressure was maintained at hypertensive levels for eighty days during administration of Vitamin D_2 did not continue to have hypertension after the drug was discontinued.

The elevation of blood pressure arising from injection of desoxycorticosterone is at present difficult to interpret. Other aspects of the physiology of various steroids of biological importance are at present undergoing intensive study all over the world and it seems likely that the part played by these substances in cardiovascular disturbances will be somewhat clarified shortly.

Buffer Nerve Hypertension

We may now turn to hypertension produced by experiments on

buffer nerves, some of which are already applicable to our understanding of the hypertensive process.

The study of hypertension produced by denervation of the cardio-aortic and carotid vasosensory zones has been pioneered by Heymans but this method has been used enough in other laboratories so that the essential facts are well known and are matters of fair agreement.

The pressure-sensitive nerve endings in the left ventricle, the arch of the aorta, and the carotid sinus are continuously sending afferent impulses to the medulla tending toward the reflex lowering of blood pressure. Bronk and Stella[10] have shown that each systole produces an increase in the frequency of afferent impulses from these regions and therefore tends to produce a vascular relaxation at the peak of systole. This work shows the rapidity of that reaction, its sensitivity, and the fact that it is normally operating in the pressure ranges which occur in the resting physiological state. The efferent pathways for these depressor effects are widespread but probably include diminution of sympathetically maintained vascular tone particularly in the splanchnic area.

Denervation of these vasosensory zones in acute experiments results in an immediate rise of blood pressure and cardiac acceleration, and Heymans and others have shown this to be largely due to a rise in sympathetic tone.

Chronic hypertension has also been produced by the denervation of these zones. For anatomical reasons the operation is difficult and uncertain particularly since the aortic depressor fibers in most species accompany the vago-sympathetic trunk and are difficult to isolate and divide. Such extensive surgery as that involved in denervating both aortic depressor zones and both carotid depressor zones is commonly attempted in a multi-stage operation. At best the final stage results in such profound cardiovascular disturbances as to endanger life immediately; and accidental interruption of vagus efferent fibers at the site of operation is liable to produce serious disturbances in the respiratory and digestive systems which may kill the animal later.

These reasons may account for the discrepancy between the pupils of Heymans, who after considerable experience are usually able to produce satisfactory chronic hypertension, and others who have commonly produced only moderate and temporary hypertension and so have been inclined to abandon the procedure before acquiring extensive

experience with it.

If the animal with chronic hypertension of this kind is sympathectomized completely, its blood pressure is restored to normal (Heymans[11]). There is no agreement (Nowak and Walker[2]) as to whether hypertension develops if the section of the moderator nerves is made originally in a sympathectomized animal. Grimson, Bouckaert and Heymans report[12] three animals in which they first performed splanchnic sympathectomy, complete except that the renal nerve supply was left intact. Next, they raised the sympathetic tone by denervation of the cardio-aortic and carotid zones. In these three animals the rise in blood pressure which ensued was believed to be due to renal vasoconstriction causing renal ischemia and thus hypertension of the Goldblatt type. These animals were later subjected to denervation of the kidneys and the blood pressure returned to normal. This type of study which involves three major operations: splanchnicectomy, moderator nerve section, and renal denervation, and requires repeated blood pressure measurements, is evidently difficult. This is a sufficient justification for the limited number of experiments reported. Unfortunately, in this experiment, the assumption is implied that the mechanism of hypertension once established is not subject to change; and therefore Heymans did not investigate the effect of varying the time interval between the establishment of the hypertension and its "cure" by renal denervation. An assurance that such animals would be cured of their hypertension by renal denervation even after a period of many months' or years' hypertension would be valuable in the consideration of the effects of prolonged elevation of blood pressure on the organism as a whole. This is a point of importance which will be discussed more fully in connection with chronic renal experimental hypertension.

The foregoing discussion of experimental hypertension of non-renal origin serves to indicate some of the lines of approach to the important question: Which of the phenomena of renal hypertension may properly be attributed solely to the change in intra-arterial pressure as contrasted with those effects due specifically to the kidney?

Experimental Renal Hypertension

The essential facts about experimental renal hypertension are well enough known that they need but the briefest recapitulation here.

Elevation of systolic and diastolic blood pressure may be regularly

produced by partial occlusion of both renal arteries by a Goldblatt clamp[1] or ligature (Wilson and Byrom[13]) or by the production of perinephritis such as can be induced by wrapping the kidney in silk or cellophane (Page[14]). Hypertension can also be produced by tightly constricting the kidney with tape according to the technique of Grollman[15] or by partial ablation of kidney tissue as described by Chanutin and Ferris.[16]

Hypertension produced by these means may be of rapid onset, rapid progress and lead to death; may be of slower onset and lead to stable chronic hypertension; or may be only temporary. This depends upon the procedure employed, the presence or absence of an intact kidney, the species under observation, and probably a number of other uncertain factors. These methods all produce hypertension but the mechanism is open to discussion and may now be examined.

Mechanism: It is usually believed that in such experiments the kidney liberates renin into the blood stream. This reacts with a part of the globulin fraction of the plasma (renin substrate—α_2 globulin) to form the vasoconstrictor substance, angiotonin, which is directly responsible for the hypertension by raising the peripheral resistance.

What part of the kidney produces the renin, and the mechanism of its liberation is uncertain.

Change of Mechanism During the Course of Experimental Renal Hypertension

Renin may be liberated very promptly in response to emergencies which reduce the pressure[17, 18, 19] but there is no certainty as to how long the kidney will continue to secrete renin. Probably in extreme circumstances the kidney can be exhausted in a few hours.* It has generally been assumed that the hypertension established by moderate renal artery obstruction and consequent renin liberation may continue indefinitely with no change of mechanism but since we know that renin substrate may be quickly exhausted by the rapid injection of renin or even by causing the kidney to liberate a large amount of this substance, it is becoming increasingly evident that this view must be reëxamined critically.

Renin in Circulating Blood: If renin, in fact, is responsible for ex-

* Shorr finds apparent exhaustion of his renal vaso-excitor material in four hours of hemorrhagic shock.

perimental renal hypertension, it should be possible to demonstrate its presence in the circulating blood. Attempts to do this have usually been unsuccessful but some investigators have detected renin in the blood stream of dogs shortly after the application of the clamp (Dell'Oro and Braun-Menendez[20]) and have remarked upon its apparent absence later.

Fasciolo, Houssay and Taquini*[21] found renal vein blood from hypertensive dogs to have a raised vasoconstrictor action on the perfused frog. Mason and Rozzell[22] were unable to confirm this. This disagreement was abolished when it was realized that the former had used dogs with newly established hypertension, the latter chronically hypertensive dogs.

It has been suggested that the animal may become increasingly sensitive to the pressor action of renin, and that therefore later hypertension might be sustained by immeasurably small amounts, but the experimental evidence does not allow of this being the sole explanation (Pickering[23]).

Hypertension from renin infusion[24] or from acute and severe limitation of renal vascular supply is of notably small magnitude and short duration and usually lasts only a few hours.

Renin is found during acute glomerulonephritis[25] but not in chronic hypertension in man. Pickering[26] has adduced other evidence indicating a fundamental difference in the mechanism of hypertension of acute and chronic nephritis.

Dock and Rytand[27] demonstrated the absence of vasoconstrictor substances in rats made hypertensive by partial nephrectomy, but they do not say how long the rats had been hypertensive. In view of all the other evidence for the humoral origin of renal hypertension their conclusion offers some support to the idea that more than one mechanism is involved in the course of renal hypertension in the rat.

Dock[28] made rabbits hypertensive by renal artery ligation, pithed them under anesthesia and found them to have blood pressures as low as normal animals similarly pithed. Since pithing lowered the blood pressure completely, he concluded that the hypertension was not mediated by a circulating pressor substance, but that the hypertension in these animals was due to a change in the "set" of the central nervous system, comparable, perhaps, with the change of the "set" of the thermal

* Dr. Taquini informs me that this question is now being reinvestigated by Dr. Fasciolo in Buenos Aires with recent improvements of technique. Preliminary correspondence with Dr. Fasciolo suggests that renin is demonstrable in normal and hypertensive animals, but that animals with long-standing hypertension have smaller quantities of renin circulating.

regulatory mechanism in lobar pneumonia.

Probably renin is not operating in rabbits after seven weeks of hypertension, so Dock's rabbits which had been hypertensive for "months" may be considered "chronic." This observation of Dock's that the nervous system is involved in late hypertensive rabbits and that a humoral system is not involved further supports the concept that the mechanism of experimental renal hypertension changes with time.

Pickering[23] showed that rabbits with recently induced renal hypertension have normal sensitivity to injected renin as contrasted with chronic renally hypertensive rabbits whose sensitivity is unusually great and prolonged. (These experiments are complicated by the fact that his observations were all made on animals shortly after complete nephrectomy, which of itself may sensitize to renin.)

Taggart and Drury[29] claimed that renal hypertension does not involve renin at all. They worked on rabbits with hypertension of two months' standing (quoted by Pickering) which therefore belonged in the "chronic" category. These rabbits were normally responsive to injected renin and when made tachyphylactic by repeated doses of renin their hypertension was not abolished. This suggests that endogenous renin was not causing their hypertension.

Wakerlin in 1943[30] showed that a series of injections of renin would prevent the development of renal hypertension if the injections were continued for some time after clamping the renal artery. Many dogs have been studied by him and others for the possible hypotensive effect of renin injections on hypertensive dogs. The results have been variable and in 1946 Wakerlin was at a loss to explain them.[31] An examination of his figures shows that renin given prophylactically or in the early stages of hypertension is usually effective, whereas extracts given later are variable and temporary in their effects. His results are compatible with the view that the injected renin uses up all the substrate and makes the animal unresponsive to its own renin and therefore abolishes the reno-humoral mechanism of hypertension. The variable results of injections given later may be, and indeed the published figures suggest that they are, due not to renin but to the temporary non-specific antihypertensive effect common to many tissue extracts (Chasis, Goldring, and Smith[32]).

The difficulty of an accurate interpretation of these experiments in the light of the dual mechanism hypothesis arises from the fact that the

TABLE I

COLLECTED RESULTS OF NEPHRECTOMY ON EXPERIMENTAL HYPERTENSION IN RATS

Authors	*Method of producing hypertension*	*Number*	*Result of nephrectomy*		
			No change or a rise	*Lowered, but not to normal*	*Return to normal*
Wilson and Byrom	Silver clip obstructing one renal artery	27	8	9	10
Friedman, Jarman, and Klemperer	Cellophane bag around one kidney	44	3	29	12
Patton, Page, and Ogden	Partial occlusion with silk tie of one renal artery	47	15	20	12
Totals		118	26	58	24
Per cent			22	49	29

Patton, Henry S., Page, Ernest W., and Ogden, Eric: The Results of Nephrectomy on Experimental Renal Hypertension, Surg. Gynec. & Obst., 76:493-497, 1943. By permission of Surgery, Gynecology and Obstetrics.

experiments were designed rather for another purpose than to test this hypothesis. Friedman[33] using three dogs of at least 54 days hypertension was unable to reduce the blood pressure by renin injections.

A number of workers (Harrison, Blalock and Mason;[34] Prinzmetal and Friedman[35]) have claimed that the ischemic kidney contains more renin than the normal kidney. Pickering, Prinzmetal and Kelsall[36] found this to be true for the newly hypertensive rabbit but not for the rabbit with hypertension of long standing. The change in the renin content of the kidneys and in the sensitivity to injected renin and the fact that renin can sometimes be found in the blood of the early hypertensive animal but not in the animal with long established hypertenson, suggest that there is a change of mechanism in the course of hypertension and that this is maintained at first by renin and later in some other way.

The Effect of Nephrectomy on Experimental Hypertension: Renal hypertension may be readily established in the rat by the partial ligation of only one renal artery leaving the other kidney intact. Removal of

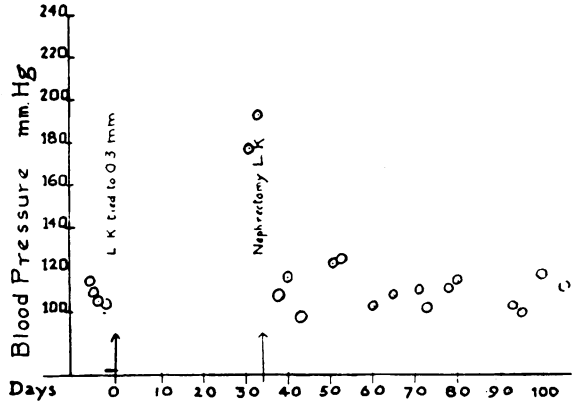

Fig. 1. Complete relief of hypertension of short duration in a rat after removal of the left kidney whose artery had been partially ligated. Right kidney intact.

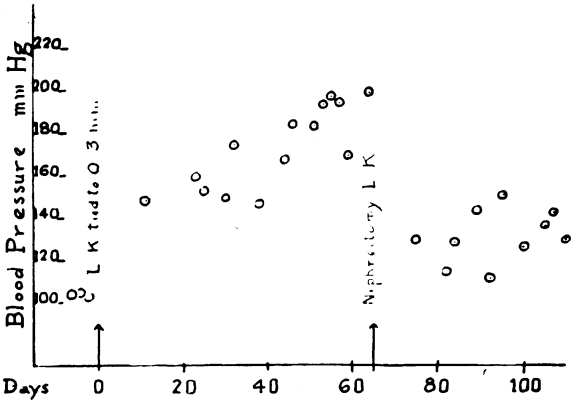

Fig. 2. Moderate improvement after hypertension of 2 months' duration.

the ligated kidney is sometimes followed by a decrease of blood pressure and sometimes not (Table I). Wilson and Byrom[13] first called attention to this and believed the *degree* of hypertension to be the determining factor.

Friedman, Jarman, and Klemperer[37] remarked on the failure of unilateral nephrectomy regularly to restore the original blood pressure in rats hypertensive from silk perinephritis. They also concluded that the restoration depends rather upon the intensity than upon the duration.

We[38] reinvestigated the effect of nephrectomy on rats made hyper-

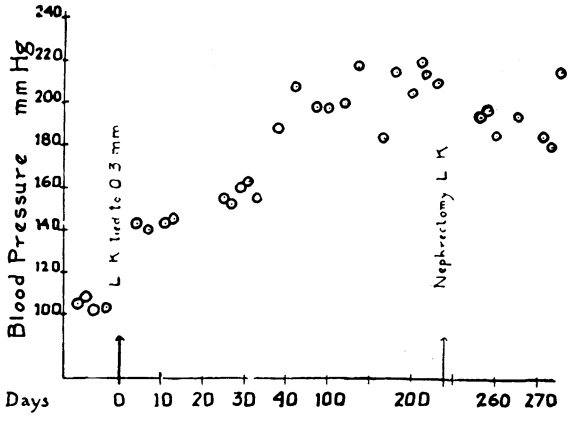

Fig. 3. No lowering of blood pressure after 7 months of hypertension. The time scale is irregular to conserve space.

TABLE II

THE RELATION OF DURATION AND SEVERITY OF HYPERTENSION TO THE EFFECTIVENESS OF NEPHRECTOMY IN RATS

Duration—wks.	*No. of animals*	*Result of nephrectomy*		
		No change or a rise	*Lowered, but not to normal*	*Return to normal*
5-10	21	2	9	10
11-45	26	13	11	2
Totals	47	15	20	12
Severity of hypertension—mm.				
140-160	26	12	9	5
161-180	11	2	6	3
181-200	7	1	3	3
Over 200	3		2	1
Totals	47	15	20	12

(Note that there is no evident relationship between the maximum blood pressure level and recovery.)

Patton, Henry S., Page, Ernest W., and Ogden, Eric: The Results of Nephrectomy on Experimental Renal Hypertension. Surg. Gynec. & Obst., 76:493, 1943. By permission of Surgery, Gynecology and Obstetrics.

tensive by partial ligation of the left renal artery. At various intervals after the hypertension was established, the left kidneys were removed. Figures 1, 2 and 3 are records selected to show that the removal of the affected kidney resulted in more or less lowering of the blood pressure according to the duration of the hypertension. Table II analyzes these experiments with respect to the effect of nephrectomy as related to both the severity and the duration of the hypertension.

These data lead to the conclusion that it is not the degree but the duration of the hypertension that counts and that the longer an animal has been hypertensive from this cause the more likely it is to remain hypertensive after the offending kidney is removed. In these experiments the obstruction of the blood supply to the kidney initiated the hypertension presumably by the renin mechanism; the maintenance of the hypertension, however, must be due to something other than the kidney which has been removed.

In view of the different interpretation of our results from the interpretations of Wilson and Byrom and of Friedman, Jarman and Klemperer, it is necessary to seek the cause of the discrepancy. Wilson and Byrom remarked upon the difficulty of interpreting their data because they cannot find a satisfactory figure to report a particular rat's blood pressure during a given period of time and so they have grouped their rats according to their judgment of their behavior. An analysis of the mean blood pressure figures given in their table does not indicate any correlation between the effect of nephrectomy and the intensity or duration of the hypertension, but a study of their grouping shows that of the 18 animals in which nephrectomy cured or substantially improved the hypertension, only three had been hypertensive for more than 10 weeks.

The data of Friedman, Jarman, and Klemperer included 44 rats of which only 4 had hypertension of seven weeks or less, fourteen of 7-10 weeks, and twenty-six of more than 10 weeks. Of the four rats with hypertension of seven weeks or less duration three returned so nearly to their original blood pressure levels as to be indistinguishable from normal (viz., 1, 7, 13 mm. above normal) but probably this experiment must be regarded as one in which the number of nephrectomies during acute hypertension is insufficient for discussion in this connection.

It seems that the failure of these two groups to come to the same conclusion as we did with regard to the effect of nephrectomy early in hypertension, may in part depend upon our having used considerably

more rats, namely 21, in the duration group of from five to ten weeks.

The significance of the conclusion that this type of hypertension is initiated by the kidney but maintained by an extra-renal mechanism was not fully realized at the time we published these data. Later, Dr. Sapirstein pointed out to us that this was a key observation in the understanding of renal hypertension, but we were unaware that Pickering[23] had already arrived at the same conclusion on the basis of observations reported by Taggart and Drury[29] on the responses to renin of normal and hypertensive rabbits.

Pickering[23] discussed the evidence for the proposition that rabbits during the first week after their renal arteries are constricted have renin hypertension but that later a "non-renal factor" plays an important, and perhaps the chief, role in maintaining the raised pressure. He lists the following three points, and I quote his words:

"In the first week after constricting the renal artery, it has been here shown that the hypertension is usually abolished completely by removing the ischemic kidney. The time taken for the arterial pressure to fall to its normal level is of the same order when the ischemic kidney is removed as it is after stopping an intravenous infusion of renin lasting 4 hours. Finally the renin content of the ischemic kidney is at this stage increased. These facts indicate that the kidney is solely responsible for the hypertension and suggest that the release of renin from the ischemic kidney is the mechanism involved."

Removal of the hypertensive rabbit's kidney after seven weeks of clamping does not abolish the hypertension. He goes on to point out that this concept of a change from a renal to a non-renal mechanism is in harmony with the finding that the newly hypertensive rabbit has a raised renin content in its hypertensogenic kidney whereas the rabbit of longer hypertension does not.

Grollman[39] reported that in the rabbit (as in the rat) nephrectomy, after ten weeks of hypertension due to renal compression, does not abolish the hypertension.

In the dog there are no large series of experiments from which one can determine whether the duration of hypertension influences the remedial value of nephrectomy. In general, by selecting from the reported experiments those in which the duration of the hypertension is reported, one may conclude that removal of the kidney causing hypertension during the first month usually abolishes the hypertension.

If the kidney is removed at three months or later, the hypertension usually persists, but before accepting this evidence as a significant differentiation between acute and chronic hypertension in the dog one must consider carefully one well-documented experiment illustrated in Goldblatt's report.[40] This experiment shows that one dog with unilateral renal hypertension of nine months' duration was completely cured of its hypertension by ipsilateral nephrectomy. The evidence in this instance seems clear cut and the importance of this experiment is so great that it seems unfortunate that only one such animal was available and that so little time was allowed to guard against spontaneous reappearance of its hypertension.

Verney and Vogt[41] give data on two hypertensive dogs nephrectomized on the 15th and 20th days respectively which shows an immediate return of blood pressure to the original level. The authors speak of an additional 4 dogs which behaved similarly but do not give the data. There seems to be little doubt from these experiments and from those of several others (Blalock and Levy,[42] Rodbard and Katz,[43] and Goldblatt[40]) (Rodbard and Katz 6 animals from 5-28 days) that removal of the kidney from a unilaterally hypertensive dog abolishes the hypertension if the nephrectomy is done within the first few weeks.

These studies on nephrectomy in dogs, rats, and rabbits indicate clearly that renal hypertension is dependent upon the kidney only in its early stages but is later maintained by some other means.

The Role of the Nervous System: At Sapirstein's suggestion we (Reed, Sapirstein, Southard and Ogden[44] and Sapirstein and Reed[45]) gave rats during the early weeks of renal hypertension Nembutal, yohimbine or F883 with no effect upon their hypertension; but animals which had been hypertensive for a number of months usually showed a lowering of their blood pressure in response to these drugs. This suggests that the mechanism maintaining the later stages of hypertension involves the nervous system, particularly the sympathetic system, and that this nervous mechanism is not operating in early hypertension. The experiments of Dock and Dock and Rytand which demonstrate that pithing completely abolishes renal hypertension falls in with this suggestion.

Jacobs and Yonkman[46] gave yohimbine to four dogs hypertensive from silk perinephritis. The administration of the drug was started fifty to seventy days postoperatively about three to four weeks after

the hypertension was established. In one of these there was an unequivocal fall of blood pressure; in two more a fall was recorded but was so small as to leave its significance in doubt; in the fourth dog no change occurred. The dog whose blood pressure fell with certainty received its medication for twice as long as the dog which showed no change, and even so neither this nor any of the four showed blood pressure restored to the preoperative level. The method of administration of the drug, the species of animal and other differences, make these experiments difficult to compare with those of Reed, Sapirstein, Southard and Ogden, but Jacobs and Yonkman's results might be summarized thus:—administration of yohimbine to newly hypertensive dogs did not consistently lower the blood pressure and never abolished the hypertension. Stated in this form they confirm the observations of Reed, Sapirstein, Southard and Ogden on rats, but the distinction between "newly" and "chronically" hypertensive dogs cannot be made from Yonkman's data though it may be cautiously inferred from other observations and from the life-span of dogs. The concept that dogs of two months' hypertension are nearing or in the "chronic" category would fit in with the work of Friedman.[37]

The Effect of Sympathectomy on Experimental Hypertension: The experiments just described with Nembutal, yohimbine and F883 suggest that the extra-renal mechanism may be concerned with the sympathetic nervous system. If this is so sympathectomy performed early in the disease might be expected to be without effect whereas it might be expected to restore the blood pressure to its normal levels if performed after renin activity had ceased.

Sympathectomy on dogs with renal hypertension fails to restore the blood pressure to normal values. Generally, the duration of the hypertension before the performance of sympathectomy has not been stated, but where this information is available the sympathectomy has been performed early in the course of hypertension at a time when its failure to affect the disease is to be expected by comparison with the failure of sympatholytic drugs to cure experimental hypertension in rats. Heymans[11] removed the sympathetic nervous system with the exception of the innervation to the kidneys, raised the sympathetic tone by moderator nerve section and observed hypertension due to the vascular clamping of the renal arteries. In these dogs the kidneys were denervated six weeks later and the blood pressure was markedly lowered. This indi-

cates that at that time renin was solely responsible for the hypertension and that the nervous system was not participating except by producing renal vasoconstriction.

Verney and Vogt[41] by compression of the renal arteries in six dogs previously sympathectomized recorded moderate to great rises in blood pressure in every case. In one of their dogs the preoperative blood pressure was 116. It rose to a peak of 142 on the 48th day after renal artery compression and had declined to 122 by the 90th day. In another dog the pressures were preoperative 105, 46th day, 170. These dogs are the two dogs followed for the longest time according to their published data and therefore suggest that in the absence of the sympathetic nervous system hypertenson of renal artery origin does not persist beyond the third month.

A number of sympathectomies have been performed in hypertensive men but the data from these do not appear to be useful for this discussion for the following reasons:

First, there are many who doubt if hypertension of the Goldblatt type commonly occurs in man and none of the few human hypertensives whose disease seems clearly to be due to this mechanism have been subjected to sympathectomy.

Second, it is rarely possible to say with any certainty how long hypertension has existed in an individual coming up for sympathectomy; probably it is always more than the period corresponding to the few weeks we have been considering in animals.

Third, many of the series of sympathectomies in man are inadequately controlled both with respect to the careful evaluation of the effects of other therapeutic measures upon the blood pressure and with respect to adequate follow-up data.

For these reasons it seems best at the present time not to attempt to analyze and evaluate the various successful and unsuccessful sympathectomies reported with regard to their bearing on this hypothesis. Undoubtedly the recent practical interest in therapeutic sympathectomy will lead to the publication of series in which the data are adequate for use and in which follow-up information can later be effectively collected.

Similarly the facts that Gregory[47] lowered the blood pressure of hypertensive patients by means of spinal anesthesia and that he demonstrated the absence of effective renal pressor activity in his hypertensive

patients must be interpreted with caution until we can be sure whether these phenomena are true throughout the course of hypertension or if not at what stages they are present.

The effects of sympathectomy, the change in response to drugs, the change in the response to nephrectomy, the change in the sensitivity to injected renin, the change in the renin content in the kidney, and the change in the findings on testing for renin in circulatig blood are six basic evidences which may now be put together to offer a tentative story of the dual pathogenesis of experimental renal hypertension.

Dual Mechanism Stated: The application of the clamp, probably by diminishing the pulsatile expansion of the kidney causes the liberation of renin and elevates the blood pressure. This raised blood pressure brings into play an extra-renal (neurogenically operated and sympathetically mediated) mechanism which maintains the vasoconstriction. The liberation of renin ceases either because the general change in vascular dynamics starts the kidney moving again or else by some other adaptation or exhaustion of the renin mechanism. The cause for the cessation of renin liberation is unknown, but the important fact which must be realized is the existence of this very fundamental change in the mechanism of hypertension.

Many experiments would have yielded much more valuable information had this change of mechanism been taken into account in planning the experiments or had the exact intervals between the establishment of hypertension and subsequent experiments on the animal been routinely reported.

The present state of the hypothesis discussed is that no critical experimental data or series of clinical observations are incompatible with this theory as applied to hypertension of the Goldblatt type, but that the critical data to support it are insufficient and are based in part on rats, which are suspect. Many scattered observations point toward the correctness of this view but critical surgical and pharmacological experiments must be performed on dogs and other species before it can be regarded as established.

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